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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/854,124	Applicant(s) Williams et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 25, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above, claim(s) *Limitations of 28-36 not drawn to SEQ ID NO:5* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment and Response to Election requirement filed August 25, 2003 (Paper No. 10) in response to the Office Action of January 21, 2003 (Paper No. 7) is acknowledged and has been entered. Claims 16-27 have been cancelled and claims 28-36 have been added. All limitations of claims 28-33 drawn to any CGI-122 gene product other than SEQ ID NO:5 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions and Claims 28-33 will be examined only as they are drawn to a method for detecting a cancerous colon cell comprising comparing the level of expression of a gene comprising the sequence of SEQ ID NO:5 to a control cancerous colon cell by hybridization or PCR. Claims 28-36 are currently under prosecution.

2. Applicants election, with traverse, of Group III, claims 20-22 in nonresponsive Paper No. 8, is based on the statement that SEQ ID NOS 5, 6, 7 are sequences encoding the same protein CG-122, which observation is described at Table 4, page 59, lines 21-23 of the application. The relationship between SEQ ID NOS 5, 6, 7 and the cDNA encoding the CGI-122 protein is shown in Appendix A. Because SEQ ID NOS 5, 6, 7 encode the same protein and since MPEP states that nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions, the restriction requirement must be withdrawn. The argument has been considered but has not been found persuasive because none of SEQ ID Nos 5, 6 or 7 encode the CGI-122 protein. The nucleic acid encoding said protein is 1174 nucleotides in length. Each of SEQ ID NOS 5, 6 and 7 are 300 nucleotides in length. Although the nucleotide sequences would be expected to

encode peptides, none of the peptides would be the same. Further, although Applicant states that Sequences 5-7 encode the CGI-122 protein and presents Appendix A suggesting that the fragments each have identity to 300 base-pair sections of the CGI-122 protein mRNA, no percent identity between SEQ ID NOS 5-7 and the CGI-122 protein mRNA sections has been presented. No objective evidence has been presented demonstrating that any of these fragments are in fact fragments of the CGI-233 protein mRNA. In particular, although Table 4, p59 states that SEQ ID NO:s 5-7 align with CGI-122 protein mRNA, Table 4 p. 59 also states that SEQ ID NO:16 aligns with HLA-E. During the prosecution of parent application 09/400,947, a search of the Geneseq database revealed that the 300 bp SEQ ID NO:16 had identity of only 14.7% over 49 nucleotides to HLA-E mRNA (please refer to the First Action on the Merits of 09/400,947 and to sequence comparison us-09-400-947.16.rng). It is clear that, although Table 4 implies identity and correlation between SEQ ID NO:16 and HLA-E mRNA, the identity is limited at best and that SEQ ID NO:16 is not in fact a fragment of the HLA_E mRNA. Given this information, in the absence of objective evidence demonstrating a 100% nucleotide by nucleotide identity between each of SEQ ID Nos 5-7 with the CGI-122 protein mRNA, it will be assumed that each of SEQ ID NOS 5-7 are not fragments of the CGI-122 protein mRNA and the groups will not be rejoined because they are distinct inventions for the reasons previously set forth.

In Paper No. 10, Applicant argues that (a) Claims 20 and 28 are both directed to methods of detecting a cancerous colon cell by comparing the level of a gene product in a test colon cell to a control level and both of the claims are drawn to the

same subject matter, (b) Applicant is not aware of any rule that prevents a group of claims corresponding to a restriction group from being replaced by a different set of claims corresponding to the same subject matter. The argument has been considered but has not been found persuasive because (a')(b') although both claims are directed to detecting a cancerous colon cell, the two claims are not drawn to the same subject matter. Claim 28 is a linking claim not originally presented. All of claims 28 and the claims dependent upon claim 28 are drawn to non-elected inventions, which for the reasons set forth previously and above, are distinct inventions and claims 28 and those claims dependent upon claim 28 will be examined only to the extent that the claims read on SEQ ID NO:5.

Further, (c) Applicant reiterates that each of SEQ ID Nos 5-7 correspond to the CGI-122 gene and a sequence alignment of SEQ ID NOS 5-7 and CGI-122 was provided with the response, (d) there is no undue burden on the Examiner to examine all of SEQ ID NOS 5-7 because they all correspond to the CGI-122 gene and all of the relevant art can be identified by searching for art relating to the single gene. The argument has been considered but has not been found persuasive because (c') contrary to Applicant's arguments, although Applicant has underlined the sequences in CGI-122 that the alignment of SEQ ID Nos 5-7 in Table 4 are drawn to, no residue-by-residue alignment of SEQ ID NOS 5-7 has been submitted and it is unknown what Applicant means when he states that SEQ ID NOS 5-7 correspond to the CGI-122 gene. What is the identity SEQ ID NOS 5-7 with the CGI-122 gene? For the reasons set forth above, were it to be found that each or any of SEQ ID NOS 5-7 did not have 100% residue by residue identity with the CGI-122 gene,

it will be assumed that those fragments are not fragments of the CGI-122 gene, (d') since it has not been demonstrated that the each of SEQ ID NOS 5-7 are in fact fragments of the CGI-122 gene, for the reasons set forth above, it would be an undue burden on the office to search each of SEQ ID NOS 5-7. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Since applicant has elected Group III, a method of detection of a cancerous colon cell comprising assaying the level of expression of a polynucleotide comprising SEQ ID NO:5 in a test colon cell compared with a cancerous colon cell control, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claims 28-33 directed to detection of a cancerous colon cell comprising assaying the level of expression of a CGI-122 gene product which reads on not only SEQ ID NO:5, but also SEQ ID NOS 6 and 7, not previously elected, have been withdrawn from consideration as being directed to a non-elected invention and a method of detection of a cancerous colon cell comprising assaying the level of expression of a polynucleotide comprising SEQ ID NO:5 in a test colon cell compared with a cancerous colon cell control will be examined. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.Newly submitted claims 28-33 are directed to an invention that is independent or distinct from the invention originally claimed for the reasons previously set forth.

4. If it were to be demonstrated that each of SEQ ID NOS 5-7 do in fact have 100% residue by residue identity with the CGI-122 gene, and if it were found that claim 28 as filed on November 15, 2002 is allowable, the restriction requirement as to the inventions linked to claim 28, that is assay of SEQ ID NO:6 and SEQ ID

NO:7 shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Specification

5. The specification on page 1 should be amended to reflect the status of the parent applications.

Claim Objections

6. Claims 28-33 are objected to as being drawn to non-elected inventions. The objection can be obviated by amending the claims to delete reference to non-elected inventions.

Claim Rejections

Claim Rejections - 35 USC § 101

7. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 28-36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by any of a specific, substantial utility or well established.

The disclosed utilities for the nucleotide fragment SEQ ID NO:5 include a method for determining diagnosis, prognosis, genetic predisposition and metastatic potential of colon cancer and detection of transcription levels and raising antibodies against expression products of the polynucleotide (p. 2, 27, 30, 32 34). However, neither the specification nor any art of record teaches what SEQ ID NO:5 or the polynucleotide that comprises SEQ ID NO:5 is, what it does, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Thus no specific utility for the claimed invention has been established. Although SEQ ID NO:5 has an established 100% identity with nucleotides 408 through 707 of human CGI-122 protein mRNA, neither the specification nor the art of record has in any way characterized the CGI-122 protein or its mRNA other than to establish that the polynucleotide is related to a gene in *C. elegans* by comparative proteomics (see Sequence Data report, us-09-854-124.5.rge, result 3). The asserted utility of SEQ ID NO:5 for the method for detecting a cancerous colon cell is based on the assertion that SEQ ID NO:5 is differentially expressed in colon cancer cell line Km12C as compared with a daughter cell line Km12L4, that is that the sequence is found at a higher concentration in the parent cell line which is poorly metastatic than in the daughter cell line which is highly metastatic (p. 56). This assertion is based on experimental evidence provided by an assay wherein millions of sequences from the mRNA libraries are hybridized under moderate stringency conditions to 300 7bp probes.

Groups of clones are brought together computationally to form "clusters. Differential expression of the cluster is assessed by determining the number of clones corresponding to the cluster in a sample compared to a control. Using these methods, SEQ ID NO:5 was isolated as being differentially expressed in the two colon cell lines (p. 53-55).

However, it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet

normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the development of artifacts in cell lines was well known in the art at the time the invention was made. For example, Drexler (Leukemia and Lymphoma, 1993, 9:1-25) specifically teaches, for the study of Hodgkin's Disease, that cell line phenotypes are frequently not concordant with that of normal hematopoietic cells and that artifactual expansion and the acquisition or loss of certain properties of the normal cells during adaptation to culture systems cannot be excluded (see abstract). Chiariello et al (Oncogene, 1998, 16:541-545) specifically teaches that the high mutation frequency previously found in glioblastoma established cell lines reflects culture condition artifacts rather than the true mutation frequency *in vivo*. Thus, it cannot be determined from the information in the specification whether it is possible to detect a cancerous colon cell by the claimed method because additional work must be done to establish whether primary colon cancers cells exhibit differential expression of SEQ ID NO:5 or a polynucleotide comprising SEQ ID NO:5 compared to normal controls. This clearly must be estabished before a comparison between cancer samples would be feasible. If there is no differential in primary normal and cancer cell expression, then it would not be possible to differentiate between normal and cancerous cells. Further, the specification does not teach what degree of "similarity" is required in order to detect

a cancerous cell. Clearly, additional work would be required in order to establish the expression level of a cancerous colon cancer cell that would be an appropriate cut-off point in order to detect cancerous colon cells and the invention does not have substantial utility. Thus, in view of the known differences in the characteristics of cell lines compared to primary tumors, the known problems with cell culture artifacts, the lack of guidance as to any differential of expression between normal and cancerous colon cells, the claimed invention does not have substantial utility because additional work must be done in order to establish a real world use for the claimed invention. Further, based on the information in the specification and in the art of record, no conclusion can be reached drawn to the utility of the claimed invention until further experimentation is done and credibility of the utility of the invention cannot be assessed. Further, it is not clear from the information in the specification how SEQ ID NO:5 was identified as the sequence to be used in the claimed method. The identification of the clusters was done by a moderate hybridization technique with a probe of seven nucleotides. The specification does not limit the members of the clusters other than to state that the clusters are, in general, from the same cDNA or closely related cDNAs (pgs. 53-55) and specifically states that with the hybridization method used, each identified oligonucleotide has some measure of specific hybridization to the specific clone identified (pgs 53-55) and specifically teaches that with the hybridization technique, artifacts occur (pgs. 53-55). Given the information in the specification, it is not possible to determine whether it is SEQ ID NO:5, or a polynucleotide that comprises SEQ ID NO:5, that is differentially expressed or whether it is a different

member of the identified cluster that is differentially expressed in the two cell lines. It is clear, based on the information in the specification, that no conclusion can be reached drawn to the utility of the claimed invention until further experimentation is done to determine whether it is SEQ ID NO:5, or a polynucleotide that comprises SEQ ID NO:5, that is in actuality differentially expressed in the cell lines or more to the point whether SEQ ID NO:5, or a polynucleotide that comprises SEQ ID NO:5 is differentially expressed in primary tumor tissue compared to normal control. Thus, the invention lacks substantial utility and credibility of the utility of the claimed invention cannot be assessed. It is noted, that libraries 15, 16 and 17 are drawn to a matched set of tissues from the same patient, that is normal colon tissue, primary colon tumor tissue and metastasized colon tumor tissue. It is further noted that libraries 18-20 are also drawn to a matched set of tissues from a different patient, that is normal colon tissue, primary colon tumor tissue and metastasized colon tumor tissue. One would wonder why, given the art recognized problems with cultured cells and the conventional nature of both hybridization and PCR techniques, that Applicant did present, in the specification as originally filed, either a simple high stringency hybridization of those tissues or why Applicant did not present a simple PCR of those tissues in order to establish the utility of the claimed invention.

Further, the asserted utility of SEQ ID NO:5 also appears to be based on the homology of SEQ ID NO:5 to the sequence encoding CGI-122. However, as set forth above, although SEQ ID NO:5 has 100% identity to a 300 nucleotide stretch of the mRNA encoding CGI-122, neither the specification nor the art of record

teaches any utility for either said mRNA or the protein encoded thereby. Thus, the claimed invention does not have a well established utility. Further, a limited search of the EST database has established that 45 ESTs identified in libraries from different human tissues exhibit 95.8 to 100% identity with SEQ ID NO:5 (see Sequence database search us-09-854-124-5.rst, pages 1-9 attached hereto) and as disclosed above, CGI-122 protein mRNA was first identified by its homology to C. Elegans. Thus it appears that the SEQ ID NO:5 sequence is ubiquitously expressed and would be expected to be expressed across many different species. Given the above, it would be reasonable to ask whether all of these detected sequences are CGI-122 protein mRNA? Would the expression of other polynucleotides with identical sequences mask an overexpression of cGI-122 proteim mRNA? Thus, additional work would be required in order to determine if the CGI-122 protein mRNA is indeed differentially expressed, as determined by the claimed assay, or whether if it were to be determined that "something" is indeed overexpressed in primary cancer cells as compared to normal controls, it might be a polynucleotide other than CGI-122 protein mRNA altogether and the invention has neither a well established utility, nor a substantial utility.

Finally, neither the specification nor any art of record teaches what SEQ ID NO:5 or a polynucleotide comprising SEQ ID NO:5 is, what it does, does not teach a relationship to colon cancer or establish any involvement of said polynucleotide in the etiology of colon cancer or any other disease. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed methods. Because the claimed invention is not supported by a

specific utility, substantial utility or a well established utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

10. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

11. Claim 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to a method for detecting a cancerous colon cell comprising detecting expression of a gene comprising SEQ ID NO:5 in a test colon cell, comparing the level of expression in the gne with a level of expression of the gene in a control cancerous colon cell.

The specification teaches as set forth above. One cannot extrapolate the teaching of the specification to the enablement of the claims because a limited search of the EST database has established that 45 ESTs identified in libraries from different human tissues exhibit 95.8 to 100% identity with SEQ ID NO:5 (see Sequence database search us-09-854-124-5.rst, pages 1-9 attached hereto) and as disclosed above, CGI-122 protein mRNA was first identified by its homology to C. Elegans. Thus it appears that the SEQ ID NO:5 sequence is ubiquitously expressed and would be expected to be expressed across many different species. Given the above, it would be reasonable to ask whether all of these detected sequences are CGI-122 protein mRNA? Would the expression of other polynucleotides with similar or identical sequences mask an overexpression of cGI-122 protein mRNA? If differential expression were found would the differential expression be found only in colon cancer cells? If differential expression were found would that expression be associated with only cancer or would it be associated with other disease types. In particular, it is notoriously well known in the art that expression of a particular gene or gene product can be associated with multiple diseases states. For example, CA125 is known to be overexpressed not only in a variety of cancer types but also to be overexpressed in response to inflammation and infection. In addition, homocysteine is also known to be overexpressed in a variety of disease states. Given the apparent ubiquitous express of polynucleotides conprising SEQ ID NO:5, given the undeveloped state of the art, it could not be predicted, nor would it be expected that the detection of a polynucleotide with the claimed method would detect a cancerous colon cell in the absence of further guidance from the

specification. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed method a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. In the event that Applicants might be able to overcome the 35 USC 101 rejection and 35 USC 112, first paragraph rejections above, claims 28-36 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of detecting a cancerous colon cell comprising detecting the CGI-122 gene product with a polynucleotide consisting of SEQ ID NO:5, wherein the control colon cell of known cancerous state has been demonstrated to have differential expression of CGI-122 compared to a normal colon cell control, does not reasonably provide enablement for detecting a cancerous colon cell comprising detecting the expression of a gene whose sequence comprises a sequence of SEQ ID NO:5, a complement thereof, wherein said detecting is with a probe which comprises SEQ ID NO:5, comprises a fragment of SEQ ID NO:5 wherein said probe comprises at least 15/150 contiguous nucleic acids of SEQ ID NO:5, wherein the assay indicates that the test colon cell is cancerous where a level of expression of SEQ ID NO:5, a complement thereof or a sequence comprising a sequence of SEQ ID NO:5 is similar to that of a cancerous cell. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to detecting a cancerous cell comprising detecting the expression of a gene which comprises **a** sequence (emphasis added) of SEQ ID NO:5, a complement thereof, by hybridization and by PCR methods and comparing this to a cancerous colon cell wherein a similarity in expression indicates that the test colon cell is cancer. This includes detection using any stringency parameters and any degree of similarity. The specification teaches that the detected polynucleotides include those detected by low stringency hybridization conditions which can be homologous or related genes (p. 4), under moderate stringency conditions (p. 54). It is noted that neither of these conditions is limiting. One cannot extrapolate the teaching of the specification to the scope of the claims because the claims encompass the detection of polynucleotides comprising non-disclosed nucleic acid sequences attached to SEQ ID NO:5, that is polynucleotides that hybridize to said polynucleotides under any stringency conditions. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing polynucleotides encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:5. The specification fails to provide an enabling disclosure for how one would use differential expression of polynucleotides assayed by the broadly claimed method in order to detect a cancerous colon cell. Further, as disclosed above, it has not been determined that the expression of SEQ ID NO:5

differs in normal cells as compared with cancerous cells. In addition, the specification does not teach what degree or range of "similarity" would be useful in order to detect a cancerous colon cell when compared with a control cancerous colon cell. Without this information, it is not possible to predict that the invention will function as claimed. The specification provides insufficient guidance with regard to these issues and it could not be predicted that the invention would function as claimed. For the above reasons, undue experimentation would be required to practice the claimed invention.

13. In the event that Applicants might be able to overcome the 35 USC 101 rejection and 35 USC 112, first paragraph rejections above, the claims 28-36 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of detection of an mRNA expression product, does not reasonably provide enablement for detection of a cancerous cell by the detection of the expression of a gene comprising SEQ ID NO:5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to detecting a cancerous colon cell by detecting the expression of a gene wherein said gene comprises SEQ ID NO:5, comprises a sequence of SEQ ID NO:5, comprises a complement of SEQ ID NO:5. This includes not only expression of mRNA but also expression of the protein product. The specification teaches that SEQ ID NO:5 is not the complete coding region of any protein and that libraries may be probed to identify coding sequences of native message which include SEQ ID NO:5 and that the polypeptide encoded by the

obtained cDNA can be expressed. One cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of whether any protein product is actually produced. Because SEQ ID NO:5 is simply a polynucleotide fragment, it is not possible to determining what the ATG start site of any protein might be and it cannot be determined if the sequence would be in-frame to encode any protein. Further, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, 31:107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Further, even were the claimed sequence attached to SEQ ID NO:5 to produce a protein product *in vivo*, it cannot be predicted that this product could be used in a method for detecting a cancerous colon cell because it cannot be predicted

that said protein product would be produced in parallel with an mRNA product. Evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 550-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2

protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Finally, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one to predict that the methods will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

14. Claim 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a method of assaying for polynucleotide expression of a gene comprising SEQ ID NO:5 and therefore the written description is not commensurate in scope with the claims drawn to assaying the expression of a gene comprising a sequence of SEQ ID NO:5, a complement of SEQ ID NO:5, a

polynucleotide comprising a fragment of SEQ ID NO:5, comprising at least 15/150 contiguous nucleic acids of SEQ ID NO:5, a polypeptide encoded by the CGI-122 protein mRNA.

Vas-Cath Inc. V. Mahurkar 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* Although drawn to the DNA art, the teaching of *Vas-Cath Inc. V. Mahurkar* is clearly applicable to the encoded protein product of the instantly claimed invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Further, *Fiers v. Revel* and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts* clearly find that adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed

genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

As drawn to the broadly claimed polynucleotide whose expression is detected in order to detect a cancerous colon cell, the specification discloses an isolated cDNA sequence, SEQ ID NO: 5, a fragment of the CGI122 protein mRNA. The claims, as written, however, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The broadly claimed genus additionally, encompasses detecting genomic sequences, as well as genes incorporating only portions of the disclosed sequence.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which

variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed as those whose level of expression is indicative of a cancerous colon cell.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences are insufficient to describe the genus of gene products that are capable of detecting a cancerous colon cancer cell. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

As drawn to the encoded polypeptide, support for a polypeptide encoded by a gene comprising SEQ ID NO:5 is found in the specification on pages 6-7 where it is disclosed that, using SEQ ID NO:5 as a probe, that complete coding sequences of native messages which include SEQ ID NO:5 could be identified. However, in the instant specification, there is no teaching of an encoded polypeptide or a teaching of any protein product encoded by a gene comprising SEQ ID NO:5. Further, for the reasons set forth above, it cannot be predicted that a translated protein product

would be produced by a gene comprising SEQ ID NO:5 or that the claimed 300 bp SEQ ID NO:5 would even encode an in-frame polypeptide. Further, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the broadly claimed expression products, that is polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the encoding polynucleotides encompassed and no identifying characteristic or property of the instantly claimed polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Therefore only a method of assaying for polynucleotide expression of a gene comprising SEQ ID NO:5 but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

15. Claims 28-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-36 are indefinite because they are all drawn to the limitation "wherein a level of expression .....in a test colon cell.....is similar to a

level of expression.....in a control cell". The term "similar" is a relative term which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 28 is indefinite because it is missing an essential step. The step that is missing is the detection of the level of expression prior to the comparison of the levels of expression.

16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 24, 2003